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# THE PREPARATION OF FLUOROCITRIC ACID AND ATTEMPTED SYNTHESIS OF FLUOROPYRUVIC ACID

By

D.E.A. RIVETT

PORTON TECHNICAL PAPER No. 319

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THE PREPARATION OF FLUOROCITRIC ACID AND  
ATTEMPTED SYNTHESIS OF FLUOROPYRUVIC ACID.

by

D.E.A. Rivett<sup>\*</sup>

1. The successful preparation of fluorocitric acid is described.
2. Attempts to synthesise fluoropyruvic acid by five different methods all failed.

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THE SYNTHESIS OF FLUOROCITRIC ACID AND  
ATTEMPTED SYNTHESIS OF FLUCROPYRUVIC ACID

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D.E.A. Rivett

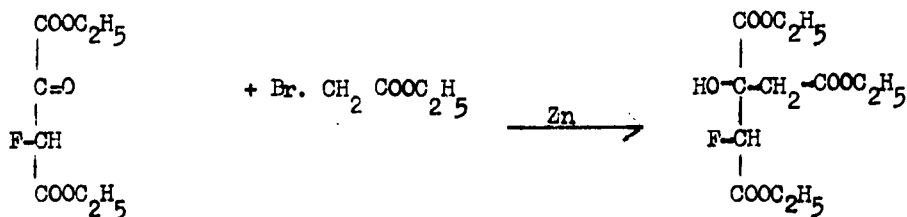
I. Synthesis of fluorocitric acid

Introduction

Fluorocitric acid is at present suspected of being the metabolite responsible for the toxicity of fluoroacetate (for a recent review see (1)). Since this material had been isolated from natural sources in only very small amounts (a few milligrams), it was very desirable to confirm its identity by synthesis. Besides, if it could be made synthetically, the very laborious isolation of the comparatively large amounts required for biochemical studies, would be unnecessary.

Method of Preparation

Of the various methods used for the synthesis of citric acid, that of Lawrence (2) appeared to be best suited for the preparation of a substituted citric acid, even though a poor yield was to be expected.



<sup>2</sup> South African Scientist attached to C.D.E.E., Porton.

The ethyl fluoroxalacetate was obtained by condensation of ethyl fluoroacetate with ethyl oxalate in the presence of sodium ethoxide. In order to obtain good yields it was important that the sodio derivative should be rapidly hydrolysed with excess acid, as otherwise free alkali (formed on addition of water) would saponify the ester and give rise to such unwanted acidic material. From the high-boiling residues a crystalline fluorine-free by-product was isolated, at times about 8% of the weight of fluoracetate used. It failed to form a 2,4 dinitrophenylhydrazone or semicarbazone. Although it reacted with p-nitrobenzoyl chloride, and with benzoyl chloride, the product could not be obtained crystalline. The acid resulting from hydrolysis was an oil. On treatment with alcoholic ammonia it furnished a crystalline material, presumably an amide. Infra-red examination of this by-product suggested that both primary alcoholic and ether linkages were present, and that it contained at least four carbon atoms joined together in a chain. The structure of this material is still undetermined.

The Reformatsky reaction between ethyl fluoroxalacetate and ethyl bromoacetate gave ethyl fluorocitrate in about 12% yield. Hydrolysis of this ester, preferably by acid, furnished the extremely hygroscopic acid, which is most conveniently handled as the barium salt.

#### Discussion

The infra-red spectrum of the synthetic barium fluorocitrate was identical with that of the barium salt of the active fraction, isolated by Sir Rudolph Peters at Oxford. The infra-red spectra of natural and synthetic barium fluorolactate and of ethyl fluorocitrate are recorded in the Appendix.

Peters has measured the inhibitor activity of sodium fluorocitrate by incubating it with kidney enzyme (for a description of the method see (1)). It had an activity of 1.13  $\mu$ g. (0.0041  $\mu$ Mol.)/unit which is half that of the isolated fluorotricarboxylic acid. With two asymmetric centres in the molecule of fluorocitric acid four diastereoisomers (two racemates) are possible. It is possible that only one racemate is active. If so, the synthetic material would possess only half the activity of the natural product.

Toxicity tests, carried out on only a few animals, indicated the following approximate toxicity figures:-

#### Toxicity of fluorocitric acid (T2234)

Rabbits, subcutaneously	LD <sub>50</sub> = 15 mg./kg.
Rabbits, intramuscularly	LD <sub>50</sub> = 4 mg./kg.
Mice, subcutaneously	LD <sub>50</sub> = 50 mg./kg.

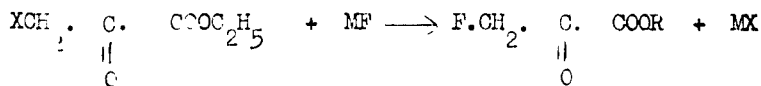
## II. ATTEMPTED SYNTHESIS OF FLUOROPYRUVIC ACID

### Introduction

Because of the important part played by pyruvic acid as an intermediate in metabolic processes it seemed likely that fluoropyruvic acid would strongly inhibit these processes in the same way as the aliphatic fluoroacids, and so be extremely toxic. Besides, as pointed out by Chenoweth (3) this material could be used to settle some of the outstanding questions concerning the mechanism of action of the fluoroacids. Although fluoropyruvic acid was not actually prepared, it was considered desirable to place on record the methods used in its attempted synthesis.

### Methods of Preparation.

1. The replacement by fluorine of halogen in a substituted pyruvic acid was obviously the method to examine first viz.

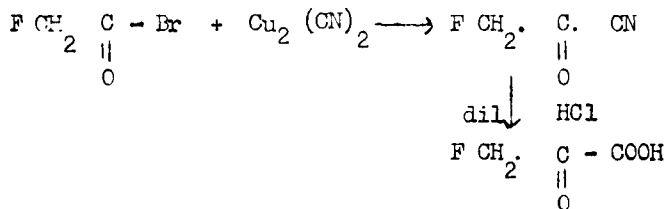


X = Cl

M = K, Na, H, NH<sub>4</sub>, antimony

However, the fluorination of ethyl chloropyruvate with either potassium fluoride, sodium fluoride - bifluoride mixture, hydrofluoric acid, ammonium fluoride or antimony trifluoride was completely unsuccessful. Unchanged chloro-body was the only isolable material from these reactions. Dr. F.L.M. Pattison (personal communication) has obtained similar results using potassium or silver fluoride on ethyl chloro- and bromo-pyruvate.

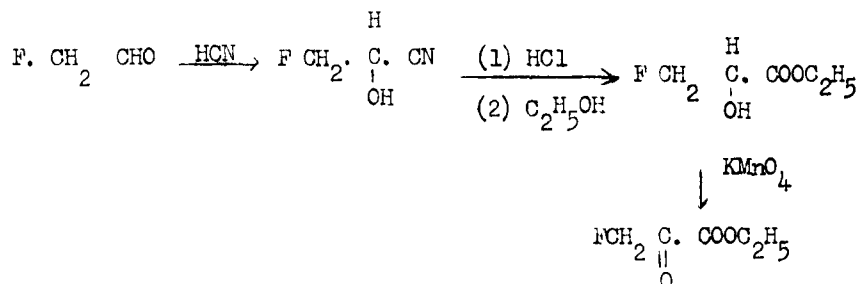
2. The standard method of preparation of 2-keto acids from acid bromides via the keto-nitrile (4) viz.



was equally unsuccessful. No liquid product could be distilled from the mixture obtained on treating fluoroacetyl bromide with cuprous cyanide. Both Sir Rudolph Peters and Dr. F.L.M. Pattison (personal communications) have obtained similar results.



3. Since ethyl lactate can readily be oxidised to pyruvate (5) the following sequence of reactions was the next considered:



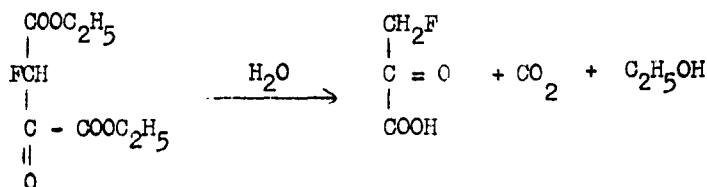
Fluoroacetaldehyde has been prepared in 6% yield by reaction of fluoroethanol with manganese dioxide and sulphuric acid (6). It was found that this material could be prepared in greatly improved yield (30% as determined by dinitrophenylhydrazone formation) by the dehydrogenation of fluoroethanol over copper-barium chromite at 330°. The crude product contained much polymer. It was treated with aqueous sodium cyanide (or hydrocyanic acid containing a little potassium cyanide) and then hydrolysed with concentrated hydrochloric acid. Only small amounts of fluorine-free material were obtained. This method having proved unsuitable, others were examined. It was found that fluorolactic ester could be prepared in 38% overall yield by oxidation of epifluorohydrin with nitric acid, followed by esterification of the acid.

Ethyl fluorolactate (T 223C) is only slightly toxic. The LD<sub>50</sub> mice, subcutaneous is 200 mg./kg. for the ester and 150 mg./kg. for the acid.

The next stage, the oxidation of ethyl fluorolactate to the pyruvate, proved very disappointing. Permanganate was considered to be the most useful oxidant and was used in a variety of ways. With free fluorolactic acid it gave fluoroacetic acid, whilst small amounts of starting material were the only isolable products obtained with ethyl fluorolactate. It might be noted in passing that lactic acid (or its ester) yielded pyruvic acid (or its ester) under identical conditions. Fluoropyruvic acid and its ester appear to be unstable and are oxidised further under these conditions. Fenton's reagent, acid dichromate and aluminium isopropoxide were equally unsatisfactory oxidising agents.

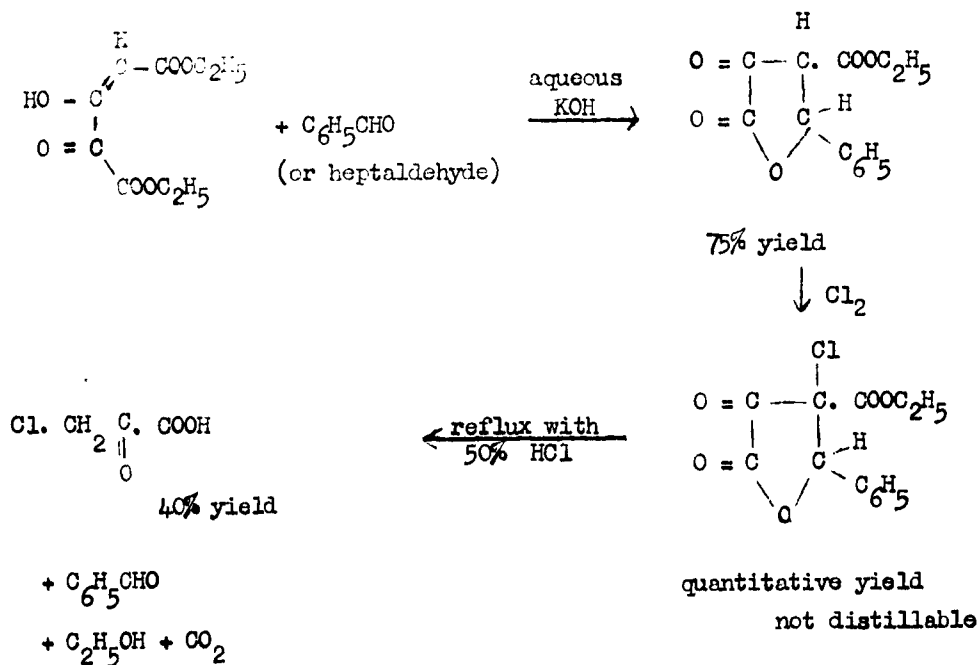
Although the oxidation of fluorolactic acid to pyruvic acid has so far not met with success it is still considered that this is a very promising route to the keto-acid. It is a question of finding the proper oxidising agent. N-bromosuccinimide and N-bromoacetamide have recently been used with signal success in the oxidation of steroidal secondary alcohols to ketones and may well be of use in this case.

4. Wislicenus (7) first described the conversion of ethyl oxalacetate to pyruvic acid by acid hydrolysis. This method has recently been applied to the synthesis of a series of  $\alpha$ -keto acids (8). Hence, hydrolysis of ethyl fluoroxalacetate might be expected to produce fluoropyruvic acid.

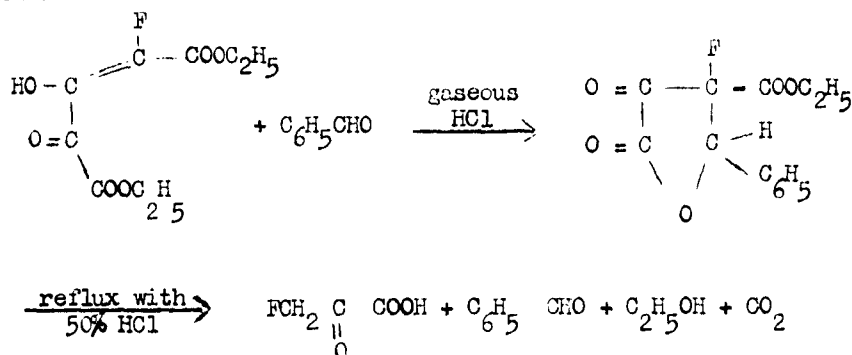


Ethyl fluoroxalacetate was readily decarboxylated on treatment with hydrochloric acid but the small amount of semicrystalline product obtained reacted only slightly with dinitrophenylhydrazine. Since there is no reason for supposing that fluoropyruvic acid does not form a dinitrophenylhydrazone (bromopyruvic acid and ethyl fluoroxalacetate do) it is considered that no more than a trace of fluoropyruvic acid could have been present in the hydrolysis product. In another experiment, in order to prevent possible decomposition of fluoropyruvic acid during distillation, the hydrolysis product was esterified before distillation, but again it gave only a slight precipitate with dinitrophenylhydrazine solution.

5. Gault and co-workers (9) have prepared chloropyruvic acid from oxalacetic ester by a rather neat method viz.



Because of the difficulty of fluorinating with elemental fluorine this procedure was adapted thus to the proposed synthesis of fluoropyruvic acid:-



A reaction appeared to occur when a mixture of ethyl fluoroxalacetate and benzaldehyde was saturated with hydrochloric acid gas, for heat was evolved and high-boiling material was produced. The crude product was hydrolysed and the acid fraction separated, but it gave only a faint precipitate with dinitrophenylhydrazine solution. Infra-red examination confirmed the absence of any carbonyl group in this material and pointed to its being an anhydride. It was not investigated further.

#### Acknowledgements

The toxicological assessments were carried out by W/Cdr. A. Muir, R.A.F., and F. Burgess. L.C. Thomas determined the infra-red spectra.

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## APPENDIX

### Experimental

#### Ethyl fluoroxalacetate

Ethyl fluoroacetate (122 g.) was added dropwise with stirring at room temperature during 1½ hours to a mixture of ethyl oxalate (174 g.) and ether (400 ml.) containing alcohol-free sodium ethoxide (from 23 g. sodium). Two days later the semi-solid product was broken up and acidified by the rapid addition of 5N-hydrochloric acid (240 ml.) cooled to -20°. Slow addition of acid results in greatly reduced yield of oxalacetate. The ether layer was separated and the residue twice extracted with ether. The combined ether extracts were washed with saturated sodium sulphate and evaporated. Distillation of the residue gave ethyl fluoroxalacetate as a colourless liquid, rapidly turning pale yellow (130 g. : 55%), b.p. 99°/3 mm. :  $N_D^{25}$  1.4203. Found: C 47.2 H 5.45:  $C_8H_{11}O_5F$

requires C 46.6 H 5.4%. It gives a reddish-brown colour with ferric chloride. It failed to form a copper enolate when shaken in chloroform solution with aqueous copper acetate. In a buffered aqueous alcoholic solution of semicarbazide it gave on standing a violet-coloured solution but no solid derivative. The 2,4 dinitro-phenylhydrazones crystallised from alcohol in yellow needles, m.p. 145°. Found: C 43.6 H 4.0 N 14.7;  $C_{14}H_{15}O_8N_4F$  requires C 43.5 H 3.9 N 14.5%.

From some preparations of fluoroxalacetate there was isolated a fairly large amount of material, b.p. 146°/1 mm. On adding ether-petroleum ether mixture and leaving at 0° this solution deposited heavy colourless needles, m.p. 69 - 70°, raised to 70 - 71° on recrystallisation from the same solvent. Found: C 46.53, 45.95, H 6.07, 5.96%. The yield was sometimes as high as 8% of the fluoroacetate used. It contained no fluorine and failed to form a dinitrophenylhydrazone in either ethanolic or acetic acid solution. It is readily soluble in ether and ethanol, insoluble in petroleum ether and water. When a solution of this material in ethanol (or methanol), saturated with ammonia, was allowed to stand crystals formed within two hours. These were separated and recrystallised from water to form tiny needles, m.p. 201° (dec.). Found: C 29.8% H 4.4% N 18.4, 17.9%.

#### Ethyl fluorocitrate

A mixture of ethyl fluoroxalacetate (36.0 g.), ethyl bromoacetate (27.3 g.) and benzene (50 ml.) was added to activated zinc (13.6 g.) at such a rate as to maintain gentle reflux. After boiling under reflux for a further hour 3 N-sulphuric acid (100 ml.) was added to the cooled solution. The benzene layer was separated, washed with aqueous sodium carbonate, dried and evaporated. The residue

distilled with some decomposition at  $120^{\circ}/10^{-1}$  mm. to give crude ester (7.6 g) and much black tar. Redistillation in vacuo furnished pure material (6.0 g; 12%);  $N_D^{25}$  1.439. Found: C 49.4 H 6.6;  $C_{12}H_{19}O_7F$  requires C 49.0 H 6.5%. It crystallised on leaving at  $0^{\circ}$  for several weeks and formed needles, m.p.  $41^{\circ}$ . The yield of ester was not improved by increasing the proportion of zinc and of bromoacetate.

The fluorocitrate (0.5 g.) was hydrolysed by boiling under reflux with 3 N-hydrochloric acid (15 ml.) for 6 hours. The acid was isolated by continuous extraction with ether and dried in vacuo for several days over phosphorus pentoxide. It is very hygroscopic and was converted to the barium salt thus. Half normal sodium hydroxide was added to neutrality followed by hot aqueous barium chloride (0.8 g. in 5 ml.). The cooled solution was filtered, the precipitate washed with cold water till free of chloride ions and the barium fluorocitrate dried at  $110^{\circ}/10$  mm. (0.50 g.) for 16 hours. Found: Ba 49.34.  $C_6H_4O_7F$   $3/2$  Ba requires Ba 49.87.  $C_6H_4O_7F$   $3/2$  Ba  $\frac{1}{2}$   $H_2O$  requires Ba 49.34%. For comparison barium citrate, prepared in the same way, was also analysed. Found: Ba 51.53.  $C_6H_5O_7$   $3/2$  Ba requires Ba 52.14.  $C_6H_5O_7$   $3/2$  Ba  $\frac{1}{2}$   $H_2O$  requires Ba 51.56%.

#### The attempted fluorination of ethyl chloropyruvate

The ethyl chloropyruvate was prepared as follows: Ethyl pyruvate, b.p.  $140 - 148^{\circ}$ , was obtained from the acid by azeotropic distillation with ethanol and toluene. A mixture of this ester (61 g.) and redistilled sulphuryl chloride (72 g.) containing a trace of benzoyl peroxide, was left at room temperature for 2 days with occasional warming. Distillation of the product in vacuo afforded ethyl chloropyruvate, b.p.  $87 - 91^{\circ}/15$  mm;  $N_D^{25}$  1.4441; yield 66g. (83 %). The recorded b.p. is  $90^{\circ}/15$  mm. (10).

In a typical fluorination experiment a mixture of chloro-ester (7.5 g.) and finely powdered dry potassium fluoride (3.0 g.) was stirred for 3 hours at room temperature. Warming the mixture even to  $60^{\circ}$  caused discolouration. Dry ether (30 ml.) was added, the solid filtered off, the solvent evaporated and the residue distilled under reduced pressure to give unchanged material (1.4 g.), b.p.  $58^{\circ}/6$  mm. When the reaction temperature was raised no distillable product was obtained. A similar lack of success attended the use of sodium fluoride-bifluoride mixture, antimony trifluoride in boiling benzene, hydrofluoric acid and of ammonium fluoride as fluorinating agents.

#### The reaction of fluoroacetyl bromide with cuprous cyanide

Fluoroacetyl bromide was prepared from fluoroacetic acid and phosphorus tribromide; b.p.  $87^{\circ}$ . The recorded b.p. is  $95 - 96^{\circ}$  (11). Cuprous cyanide was prepared in a fume cupboard by adding, with shaking, an aqueous solution of potassium cyanide (2 mols.) to a

solution of copper sulphate (1 mol.), the temperature of the mixture being kept below  $25^{\circ}$  by cooling. The precipitate was filtered off, washed and dried for 2 days in vacuo over phosphorus pentoxide. It reacted satisfactorily with acetyl bromide.

Cuprous cyanide (11.0 g.) was added in portions through the condenser to fluoroacetyl bromide (17.0 g.) contained in a flask fitted with a reflux condenser and drying-tube. The mixture was heated for 3 hours in an oil-bath at  $130^{\circ}$ . The apparatus was then set for downward distillation under a vacuum of 40 mm. but no distillate was obtained.

#### The preparation and oxidation of fluorolactic ester

##### (a) Attempted preparation from fluoroethanol

The preparation of the catalyst and the procedure used for dehydrogenation are described in Vogel's book (12). Because the condenser tended to become blocked with the large amount of polymer formed it was dispensed with, and a wide tube, leading into a long-necked flask and cooled to  $-25^{\circ}$ , was connected to the end of the combustion-tube. Less polymer formed on working under reduced pressure and later experiments were conducted at about 30 mm. pressure.

In a typical experiment fluoroethanol (30 g.) gave 20 g. of product. On gentle warming the polymer present formed a flak. The supernatant liquid contained 55% of aldehyde as determined by means of 2,4-dinitrophenylhydrazine (13). Hydrogen cyanide (13 g.) was added, no heat was evolved, and the tightly stoppered flask was left at room temperature for 4 days. After low-boiling material had been removed under water-pump vacuo concentrated hydrochloric acid (40 ml.) was added. The mixture became warm, was cooled in running water, and then heated for 4 hours at  $65^{\circ}$ . Water (40 ml.) was added, the acid isolated by continuous extraction with ether and distilled in a short-path still at  $120 - 150^{\circ}/10^{-2}$  mm. to give a straw-coloured distillate (3.1 g.) which contained no fluorine.

N-Propanol, treated in the same way (except that the dehydrogenation was carried out at atmosphere pressure) gave  $\beta$ -hydroxybutyric acid in 33% yield.

##### (b) Preparation from epifluorohydrin

The epifluorohydrin was prepared by heating epichlorohydrin in a rotating autoclave (200 r.p.m.) at  $190 - 205^{\circ}$  for 12 hours with dry powdered potassium fluoride (1.5 mols.) (c.f. (11)). The temperature must not be raised above  $210^{\circ}$  otherwise extensive polymerisation occurs. After cooling, the liquid contents of the autoclave was distilled out under a vacuum of 14 mm., the receiver being cooled to  $-10^{\circ}$ . The product was twice distilled through a 15" Fenske column to give epifluorohydrin, b.p.  $85^{\circ}$ ,  $n_D^{25}$  1.3675, in 34% overall yield, 57% yield calculated on recovered epichlorohydrin.

The oxidation of the epifluorohydrin was carried out as follows. Epifluorohydrin (58 g.) was dropped during 15 minutes with stirring into a mixture of water (58 ml.) and nitric acid (S.G. 1.42; 20 ml.) contained in a 500 ml. flask, fitted with a double-surface condenser, glass mercury-seal stirrer and separating funnel and heated on a steam-bath. More nitric acid (100 ml.) was then added, the mixture heated for a further 3 hours and left overnight at room temperature. Water and nitric acid were removed under water-pump vacuo; the presence of traces of hydro-fluoric acid results in the formation of small amounts of silica. Hot water (1 l) was added, followed by powdered calcium carbonate until effervescence ceased (about 70 g.). The precipitate of calcium oxalate was filtered off at 60°, the filtrate acidified with concentrated hydrochloric acid (100 ml.) and the fluorolactic acid isolated by continuous extraction with ether. On esterification by azeotropic distillation with ethanol and benzene it gave ethyl fluorolactate (40 g; 38%), b.p. 74°/12 mm.;  $N_D^{25}$  1.4078. Found: C 44.4 H 6.7;  $C_5H_9O_3F$  requires C 44.1 H 6.7%. Esterification of the acid by boiling under reflux for 5 hours with absolute ethanol (200 ml.) containing 5% hydrochloric acid gave a 36% overall yield of the ester.

The p-nitrobenzoate of ethyl fluorolactate formed needles, m.p. 67 - 67.5°, after two recrystallisations from 40/60 petroleum ether. It was dried at 40°/2 mm. for 10 hours before analysis. Found: C 50.7 H 4.4;  $C_{12}H_{12}O_6NF$  requires C 50.5 H 4.2%. The benzoate is an oil which could not be crystallised.

A portion of the ester was hydrolysed to the acid which distilled at 100°/0.1 mm. Fluorolactic acid formed a p-bromophenacyl ester, m.p. 126°, after three recrystallisations from methanol. Found: C 42.6 H 3.5;  $C_{11}H_{10}O_4BrF$  requires C 43.3 H 3.3%.

Attempts to prepare fluorolactamide by saturation of the ester with ammonia gave a brown oil which could not be crystallised.

(c) Attempted oxidation of fluorolactate to fluoropyruvate.

The oxidation of fluorolactate with permanganate was performed essentially as described in Organic Syntheses (5), excepting that benzene was substituted for petroleum ether because of the insolubility of the ester in the latter. Also, the amount of sodium dihydrogen phosphate was increased so as exactly to neutralise the alkali formed. However, from the reaction between ester (6.8 g) benzene (50 ml.), potassium permanganate (6.6 g.), sodium dihydrogen phosphate (6.6 g) and saturated magnesium sulphate (15 ml.) only unchanged fluorolactate (3.6 g.) identified by boiling point and refractive index, was isolated.

#### The acid hydrolysis of ethyl fluoroxalacetate

5N-hydrochloric acid (90 ml.) was added carefully with shaking to ethyl fluoroxalacetate (12 g.), the temperature of the reactants being kept below  $40^{\circ}$  by cooling. After standing at room temperature for 2 days the mixture was heated at  $70 - 80^{\circ}$  until effervescence ceased (about 1 hour), cooled and extracted continuously with ether. The dried ether extract was evaporated and distilled under reduced pressure to give a semicrystalline solid (1.5 g.), b.p.  $63^{\circ}/2$  mm. It could be recrystallised with difficulty from benzene and formed hygroscopic needles, m.p. about  $72^{\circ}$ . Found: equivalent weight 83;  $C_5H_3O_3F$  requires equivalent weight 106. It contained fluorine but gave only a slight precipitate with a 2N-hydrochloric acid solution of 2,4-dinitrophenylhydrazine.

In another experiment the acid obtained from the hydrolysis of the fluoroxalacetate was esterified by azeotropic distillation with benzene and ethanol and then distilled in vacuo. The resulting ester had b.p.  $75^{\circ}/15$  mm.,  $N_D^{25}$  1.4078. Found: C 45.4 H 6.1;  $C_5H_7O_3F$  requires C 44.8 H 5.3%. When hydrolysed to the acid and treated with dinitrophenyl-hydrazine solution only a slight milkiness formed.

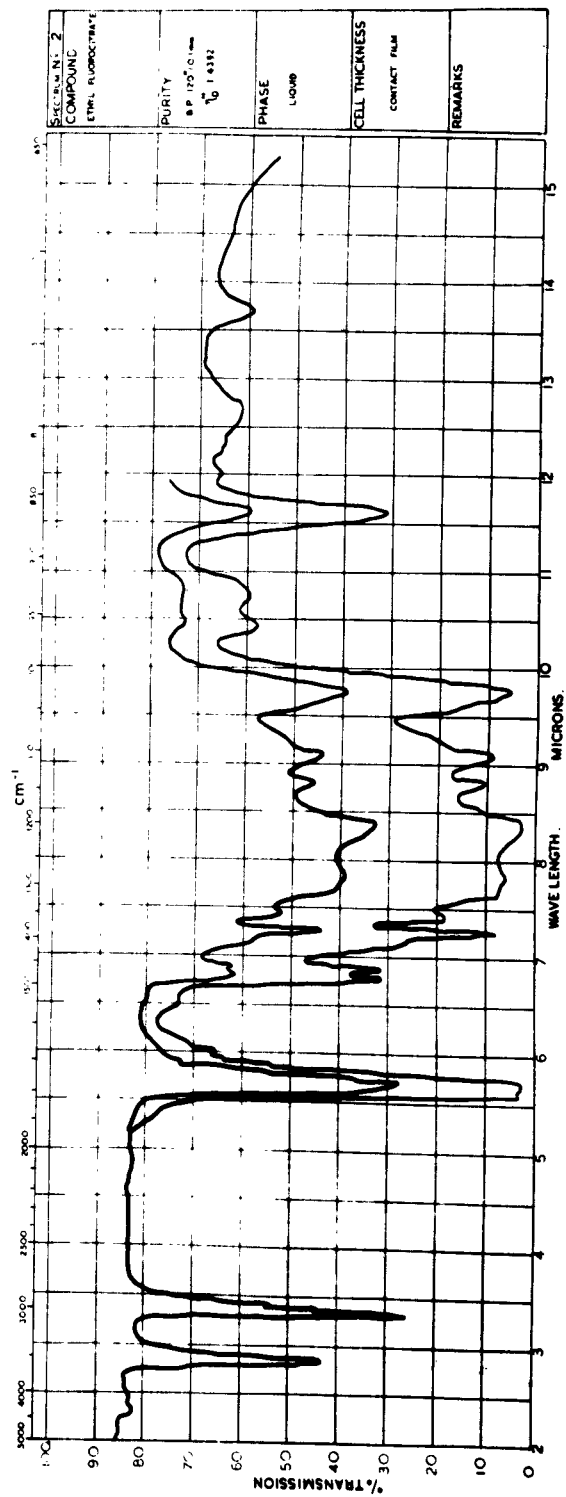
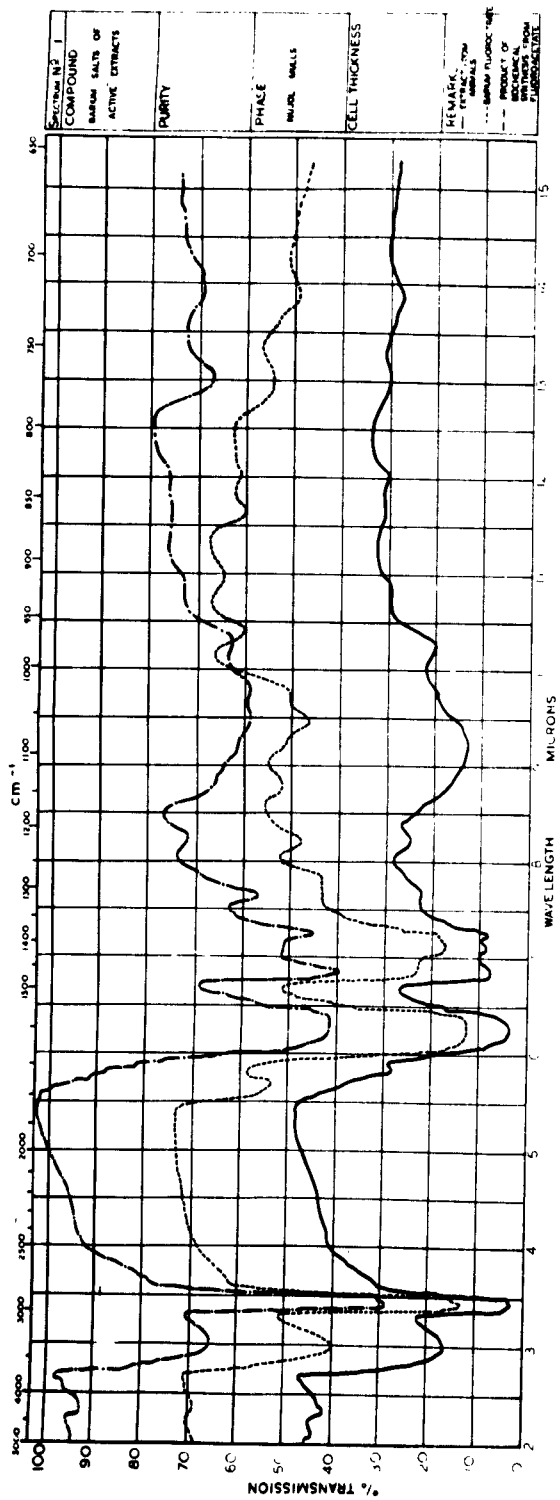
#### Condensation of ethyl fluoroxalacetate with benzaldehyde and hydrolysis of the product.

When a stream of dry hydrochloric acid gas was passed through a mixture of ethyl fluoroxalacetate (13.4 g.) and benzaldehyde (8.0 g.) for  $\frac{3}{4}$  hour (c.f. (14)) it increased in temperature and turned first light brown, finally light green in colour. After 7 days at room temperature 5N-hydrochloric acid (80 ml.) was added, the solution boiled under reflux for 4 hours, and then extracted continuously with ether. The ether extract was neutralised with aqueous sodium bicarbonate, the upper layer containing benzaldehyde withdrawn and the lower layer acidified and extracted continuously with ether. The ether solution was dried, evaporated and distilled in vacuo through a short-path still to give a liquid, b.p.  $130^{\circ}/15$  mm. (1.2 g.), which partly crystallised on standing. It did not react with dinitrophenylhydrazine solution.



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Availability Open Document, Open Description, Normal Closure before FOI Act: 30 years  
Former reference (Department) PTP-319  
Held by The National Archives, Kew

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